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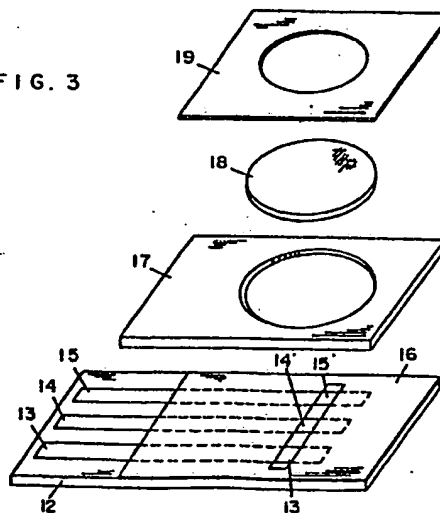
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⑤ BIOSENSOR AND METHOD OF MANUFACTURING SAME.

⑦ The electrode systems (13, 14, 15) consisting mainly of carbon on an insulated substrate (12), and the surfaces of said electrode systems are coated with an insulating layer (16) while parts (13', 14', 15') thereof being exposed. A porous member (18), which retains oxygen and electron receptors thereon, and a retainer frame (17) are then provided on the upper surface of the resultant product. A cover (19) having an opening with the diameter smaller than that of the porous member (18) is then placed on the resultant product, and all of these parts are combined integrally. Owing to such a construction, an inexpensive disposable biosensor capable of carrying out a measuring operation easily can be obtained. When heat-treated at 60-170°C for 1-8 hours during the formation of the electrode systems, the preservation stability of the biosensor can be improved. By subjecting the surfaces of the measuring electrodes to a protein adsorption treatment, the dispersion of response currents can be prevented.

FIG. 3



SPECIFICATION

TITLE OF THE INVENTION:

BIOSENSOR AND METHOD FOR MAKING THE SAME

TECHNICAL FIELD:

5 This invention relates to a biosensor for quantitatively determining specific components in various biological samples accurately, rapidly and simply and also to a method for making the same.

TECHNICAL BACKGROUND:

10 In recent years, a variety of biosensors have been developed using specific catalytic actions of enzymes, and their applications to the clinical and examining field have been attempted. As inspection items and specimens are now increasing, there is a demand for biosensors which permit
15 rapid and accurate measurements.

 With a sensor for glucose, for instance, since diabetics are drastically increasing in number, the measurement and control of blood-sugar levels by hitherto employed procedures in which the blood is centrifugated to
20 obtain plasma and subjected to the measurement, takes a relatively long time. Thus, a sensor of the type which enables one to measure it with the whole blood is now required. In the simplest form, there is known a sensor which includes, similar to a urine test paper, a support and
25 a carrier formed on the support and containing an enzyme

reacting only with glucose and a dye which undergoes a change at the time of the enzyme reaction or with a product formed during the enzyme reaction. The blood is added to the carrier, and a change of the dye after a certain period of time is measured visually or optically. However, this system is disadvantageous in that colored matters in the blood greatly interfere with the measurement, resulting in a low accuracy.

In order to overcome the above, there has been proposed a multi-layered carrier for analysis as is particularly shown in Fig. 1 (Japanese Laid-open Utility Model Application No. 54-178495). This carrier includes a transparent support 1, on which are superposed a reagent layer 2, a developing layer 3, a waterproof layer 4 and a filtration layer 5 in this order. When a blood sample is dropped from the above, solid matters in the blood such as red blood cells, platelets and the like, are initially removed by means of the filtration layer 5, followed by uniform infiltration from a small hole 6 of the waterproof layer 4 toward the developing layer 3. At the reagent layer 2, the reaction is caused to proceed. After completion of the reaction, light is applied from the direction of the arrow through the transparent support 1 to measure a substrate concentration by spectroscopy. As compared with the known simple stick carrier, this carrier has a

complicated structure but the removal of blood cells is more improved. However, it takes a long time for the infiltration and the reaction of the blood corpuscles, so that the waterproof layer 4 for preventing the sample from drying is essential, with an attendant problem that the equipment and the carrier become complicated.

On the other hand, a biosensor of the type as shown in Fig. 2 has been proposed (for example, in Japanese Laid-open Patent Application No. 59-166852) as a system in which a specific component in a biological sample is quantitatively determined in high accuracy without resorting to any procedures such as dilution of a liquid sample and agitation. This biosensor includes an insulative substrate 7, a measuring electrode 8 and a counter electrode 9, which have, respectively, leads 10, 11, embedded in the substrate 7, and a perforated body 12 which covers exposed portions of these electrodes and carries an oxydo-reductase and an electron acceptor. When the liquid sample is dropped on the perforated body, whereupon the oxydo-reductase and the electron acceptor in the perforated body dissolve in the sample liquid, thus permitting the enzyme reaction with a substrate in the liquid sample to proceed. As a result, the electron acceptor is reduced. After completion of the enzyme reaction, the reduced electron acceptor is electrochemically oxidized and a concentration of the

substrate in the liquid sample is determined from a current for the oxidation.

In this arrangement, although the measurement can be performed simply by replacing the perforated body every measurement, additional procedures, such as washing, are undesirable for the electrode system. If parts including the electrodes could be disposably replaced whenever the measurement is effected, the measuring procedure would become very simple but the system would be very expensive in view of the electrode materials such as platinum and the arrangement. Although the platinum electrodes may be formed by a sputtering method or a vacuum evaporation method, they are still expensive in view of the manufacture.

In order to measure a specific component in a biological sample such as blood simply, rapidly and in high accuracy, a desirable type of sensor is one which can yield measurements only by addition of a liquid sample to the sensor without dilution or weighing. In addition, a sensor of the disposable type is also desirable which does not involve any procedures such as washing, sampling, and the like.

DISCLOSURE OF THE INVENTION:

A biosensor according to the invention is of the type which comprises an insulative base and an electrode unit or system comprising, at least, a measuring electrode and a

counter electrode and in which an oxydo-reductase, an electron acceptor and a liquid sample are reacted with one another and a variation in concentration of a substance occurring during the reaction is electrochemically detected
5 by means of the electrode system to determine a concentration of a substrate in the sample liquid. In this biosensor, the electrode system is made primarily of carbon and is covered with a perforated body carrying an oxydo-reductase and an electron acceptor therein so that the
10 electrode system and the base are integrally constituted. The electrode surface has been preliminarily coated with a protein, so that an influence of proteins in samples, such as blood, on the electrodes by adsorption can be mitigated. Once the carbon electrodes have been subjected to a heat
15 treatment in a predetermined temperature range, the electrodes become stabilized with respect the activity or state on the exposed portions, thereby improving storage stability. Moreover, when the electrode system and the base are formed integrally with not only the perforated body
20 having an oxydo-reductase and an electron acceptor, but also a sample addition layer, a filtration layer and a liquid-retaining layer, one can cause the enzyme reaction with a substrate in liquid sample and the electrode reaction of the electron acceptor to proceed more smoothly.

25 According to the invention, there is provided a

biosensor of the disposable type including a disposable electrode system, by which a substrate concentration in a sample liquid, e.g. a glucose concentration in the blood, can be measured by a simple procedure of adding the liquid sample, in a rapid and highly accurate fashion without dilution and weighing.

BRIEF DESCRIPTION OF THE DRAWINGS:

Fig. 1 is a schematic view of a known sensor for glucose; Fig. 2 is a schematic view of a known sensor for glucose using an enzyme electrode; Fig. 3 is a schematic view of a biosensor according to one embodiment of the invention; Fig. 4 is a longitudinal section of the biosensor shown in Fig. 3; Figs. 5, 6 and 7 are, respectively, response characteristics of the biosensor shown in Fig. 3; Fig. 8 is a schematic view of a biosensor according to another embodiment of the invention; and Fig. 9 is a longitudinal section of the biosensor shown in Fig. 8.

BEST MODE FOR CARRYING OUT THE INVENTION

Example 1

A sensor for glucose is described as one embodiment of a biosensor. Fig. 3 shows one embodiment of a sensor for glucose and is an exploded view for constituent parts. A conductive carbon paste containing a resin binder is printed, by screen printing, on an insulative base 12 made of polyethylene terephthalate in the form of parallel stripes,

followed by heating for drying to form an electrode system consisting of a counter electrode 13, a measuring electrode 14 and a reference electrode 15. The electrode system is partially covered, after which an insulative paste mainly
5 composed of a polyester is printed in the same manner as described above while leaving portions 13', 14' and 15' (each 1 mm² in area) of the respective electrodes acting as electrochemical sites, followed by heating to form an insulative layer 16. Subsequently, the exposed portions
10 13', 14' and 15' are polished and subjected to heat treatment in air at 100°C for 4 hours.

Thereafter, a punched holding frame 17 of a synthetic resin such as a polyester is adhered to the insulative layer 16. A perforated body 18 having an enzyme and an electron
15 acceptor is placed in the hole of the frame 17 so that the electrodes 13', 14' and 15' are completely covered. A resin cover 19 having an opening which is smaller than the outer diameter of the perforated body 18 is adhered, thereby obtaining an integrally assembled sensor. The sectional
20 view of this biosensor taken along the the measuring electrode 14 is shown in Fig. 4. The perforated body used above is fabricated as follows: a nylon non-woven fabric is provided as a base; the base is dipped in a solution of 200 mg of glucose oxidase as an oxydo-reductase and 400 mg of
25 potassium ferricyanide as an electron acceptor dissolved in 1

ml of a phosphate buffer solution containing 0.25 wt% of a surface active agent (polyethylene glycol alkylphenyl ether) and having a pH of 5.6 and immersed in ethanol containing 0.25 wt% of a surface active agent for crystallization; and
5 the thus immersed base is dried under reduced pressure to obtain a perforated material.

A glucose standard solution provided as a liquid sample was dropped in the perforated body of the thus fabricated sensor. Two minutes after the dropping, a pulse voltage of
10 700 mV based on the reference electrode was applied, by which the measuring electrode was polarized anodically.

In this case, the added glucose reacts with potassium ferricyanide by the action of the glucose oxidase contained in the perforated body 18 to form potassium ferrocyanide.
15 Upon the application of the pulse voltage for the anodic polarization, a current for the oxidation in proportion to a concentration of the formed potassium ferrocyanide is obtained. This current value corresponds to a concentration of the glucose substrate.

20 Fig. 5 shows the relation between a current obtained 10 seconds after application of the voltage and a glucose concentration as one of response characteristics of the sensor, revealing a very good linearity.

Example 2

25 The procedure for fabricating the sensor for glucose as

described in Example 1 was repeated except that the thermal treatment after polishing of the carbon electrodes was effected at 100°C, 70°C, 60°C and 50°C, and that the heat treatment was not effected, thereby fabricating a plurality of sensors for each case. These sensors were kept at 30°C and their variation in response to the glucose standard solution was determined. Fig. 6 shows a variation of a response current relative to an initial response current taken as 100% for the sensors using the electrodes thermally treated at different temperatures. As will be clearly seen from the figure, the variation of the response accompanied by the storage is not so great when the treating temperature is 60°C or higher. However, such a variation is great for 50°C and also for the non-treatment. This is considered to result from the fact that the exposed surface portion of the polished carbon printed electrodes is not stabilized. When the electrode surface was not polished, a response current was about 1/3 of that of polished electrodes. The difference in response current between the polished and non-polished electrodes is considered to be attributed to partial covering of the carbon surface with a resin component contained as a binder in the paste. Polishing can remove the resin binder from the carbon electrode surface and can uniformly smooth the electrode surface. In addition, the heat treatment at temperatures not lower than

60°C, preferably 60 - 170°C, for 1 - 8 hours permits the the exposed electrode portion to become stabilized.

According to our experiments, when the heat treatment was effected at a temperature of 70 - 150°C for 4 hours, good results were obtained in that the variation in response current after storage was very small.

Good results cannot be obtained when the heat treatment is effected at temperatures not higher than 50°C as discussed above. On the contrary, the heat treatment at temperatures higher than 170°C should rather be avoided because the polyethylene terephthalate substrate of the sensor tends to undergo thermal deterioration and the resin binder in the carbon paste is apt to deteriorate.

Example 3

Similar to the procedure described in Example 1, electrodes were formed on an insulative base and, after polishing, were thermally treated at 100°C for 4 hours. Thereafter, an aqueous solution of alubmin (50 mg/ml) was dropped over the surface of the electrode portions 13', 14' and 15' and allowed to stand for 5 - 10 minutes, followed by washing with water to remove an excess of the alubmin and drying. By the above procedure, the alubmin was adsorbed on the respective electrode surfaces.

After formation of the electrode system partially covered with the alubmin, sensors for glucose were made in

the same manner as in Example 1.

A serum sample containing about 90 mg/dl of glucose was dropped in position of the 10 glucose sensors fabricated above. After 2 minutes, a pulse voltage of 700 mV was applied for measurement in the same manner as in Example 1. Good reproducibility was attained as shown in A in Fig. 7. On the other hand, glucose sensors were fabricated in the same manner as described above but using electrodes not subjected to adsorption with alubmin. These sensors were subjected to measurement in the same manner as set forth above. As shown in B in Fig. 7, the variation of the response current is greater than that of A. A and B are both indicative of the response current for 10 glucose sensors fabricated in the same manner, but the difference in reproducibility depending on the adsorption treatment is considered to ascribe to the difference in adsorbability of adsorbates, such as proteins, in the serum sample on the electrodes. As is seen from A, the electrodes adsorbing sufficiently with alubmin can prevent the response current from scattering.

Instead of alubmin, an aqueous solution of glucose oxidase (100 mg/ml) was used for the treatment in the same manner as described above, with the result that the response characteristic of a high reproducibility was obtained.

The proteins to be adsorbed should not be construed as

limiting to alubmin and glucose oxidase used in the above example. If at least measuring electrode among the electrodes is subjected to the adsorption treatment, similar results are obtained.

5 Example 4

In the same manner as in Example 3, an alubmin-coated electrode system was formed on an insulative base. Fig. 8 shows an exploded view of a sensor prior to assembling. A liquid-retaining layer 23 made of a perforated rayon non-woven fabric is placed, while
10 controlling the height by means of two resin plates 22 serving as a spacer, in order to cover an electrode system therewith. Then, a filtration layer 21 made of a polycarbonate film and having a pore size of 1 μ m is mounted
15 on the layer 23 and fixed with a holding frame 17. An enzyme and electron acceptor-bearing perforated body 18 and a sample addition layer 20 made of a cellulose non-woven fabric, both in the form of a disk, are placed in the hole of the holding frame 17. A resin cover having an opening
20 which has a diameter smaller than the outer diameters of the perforated disk body 18 and the sample addition layer is adhered, thereby obtaining an integral combination. A sectional view of the thus integrally combined biosensor taken along the measuring electrode 1 is shown in Fig. 9.

25 In the same manner as in Example 1, glucose oxidase and

potassium ferricyanide were incorporated in the perforated disk body 18. Glucose sensors using this perforated body 18 were fabricated. The blood (whole blood) was added to each sensor, whereupon it was rapidly spread over and through the entire surface of the sample addition layer 20. While the enzyme and potassium ferricyanide in the perforated body 18 were being dissolved in and permitted to react with the blood, red cells were filtered by means of the filtration layer 21. The resultant filtrate alone was absorbed in the liquid retaining layer 23, allowing a reaction solution to be collected on the electrode portions 13', 14' and 15' in an amount enough to cause the electrode reaction to proceed. In this manner, the glucose in the blood reacted in the same manner as in Example 1 and a concentration of the glucose could be detected through the electrode system.

It will be noted that the technique of integral assembling of a biosensor of the invention is not limited to those shown in the examples with respect to the shape and combination of the frame, the cover and the like.

The types of materials for the liquid-retaining layer, the sample addition layer and the filtration layer are not limited to those shown in the examples, but any materials which meet the purposes of the invention may be used.

On the other hand, reference has been made to, in the above examples, the three-electrode system, but the

measurement would be possible using a two-electrode system consisting of a counter electrode and a measuring electrode.

As for the electron acceptor incorporated in the perforated body 18, the potassium ferricyanide used in the examples is convenient because the reaction proceeds stably. On the other hand, p-benzoquinone is suitable for high-speed measurement because of the high reaction rate. Alternatively, 2,6-dichlorophenol indophenol, methylene blue, phenazine methosulfate, potassium beta-naphthoquinone-4-sulfonate and the like may also be used.

The sensors described in the examples may be applied not only to glucose, but also to systems relating to oxydo-reductases, for example, as an alcohol sensor, a cholesterol sensor or the like. Glucose oxidase has been used as an oxydo-reductase, but other enzymes such as, for example, alcohol oxidase, xanthine oxidase, cholesterol oxidase and the like may also be used.

INDUSTRIAL UTILITY:

The biosensor of the invention can be use to measure a specific component in various biological liquid samples rapidly, accurately and simply and has very high utility in clinical examinations.

WHAT IS CLAIMED IS:

1. A biosensor of the type which comprises an insulative base having an electrode system which includes at least a measuring electrode and a counter electrode and in which a variation in concentration of a substance occurring during reactions between an oxydo-reductase, an electron acceptor and a liquid sample is electrochemically detected to measure a concentration of a substrate in said sample liquid, characterized in that said electrode system is made primarily of carbon and is covered with a perforated body having said enzyme and said electron acceptor and that said perforated body is integrally combined with said electrode system and said base.
2. A biosensor according to Claim 1, wherein said electrode system includes the measuring electrode, the counter electrode and a reference electrode.
3. A biosensor according to Claim 1, wherein said electrode system is formed by application or printing of a carbon paste.
4. A biosensor according to Claim 1, wherein the surface of at least the measuring electrode is covered with a protein.
5. A biosensor according to Claim 4, wherein said protein is albumin or glucose oxidase.
6. A biosensor of the type which comprises an

insulative base having an electrode system which includes at least a measuring electrode and a counter electrode and in which a variation in concentration of a substance occurring during reactions between an oxydo-reductase, an electron acceptor and a liquid sample is electrochemically detected to measure a concentration of a substrate in said sample liquid, characterized in that said electrode system is made primarily of carbon and is covered with a perforated body having said enzyme and said electron acceptor, a sample addition layer and a liquid-retaining layer superposed in this order and that said perforated body, said sample-accepting layer and said liquid-retaining layer are integrally combined with said base.

7. A biosensor according to Claim 6, wherein a filtration layer is provided on the liquid-retaining layer covering said electrode system.

8. A biosensor according to Claim 6, wherein the surface of said electrode system made of a carbon paste is covered with a protein.

9. A biosensor according to Claim 6, wherein the electrode system mounted on said insulative base and primarily made of carbon is covered with the liquid-retaining layer whose height is regulated with two resin plates; a filtration layer, the perforated body and the sample addition layer which are held with a resin holding

frame are placed on the liquid-retaining layer, and said holding frame is fixed to said base; and a resin cover is provided on the upper surface of said holding frame and has an opening whose diameter is smaller than outer diameters of said perforated body and said sample addition layer.

10. A method for making a biosensor characterized by comprising providing an insulative base, printing or applying a carbon paste on said base to form an electrode system including, at least, a measuring electrode and a counter electrode, polishing the surface of the respective electrodes and subjecting the polished electrodes to a thermal treatment at a temperature of 60 - 170°C for 1 - 8 hours, covering the electrode system with a perforated body having an oxydo-reductase and an electron acceptor therein, and integrally combining said perforated body with said electrode system and said insulative base.

11. A method for making a biosensor according to Claim 10, wherein the thermal treatment is effected at a temperature of 70 - 150°C for 4 hours.

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FIG. 1

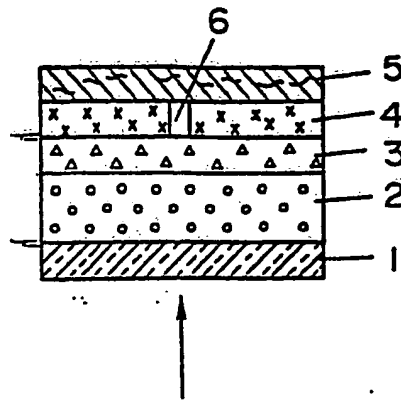


FIG. 2

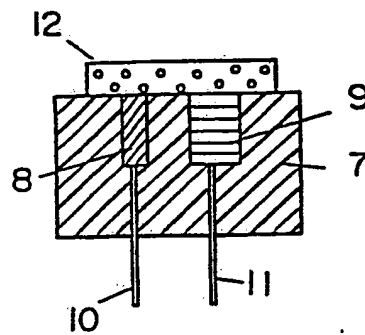


FIG. 3

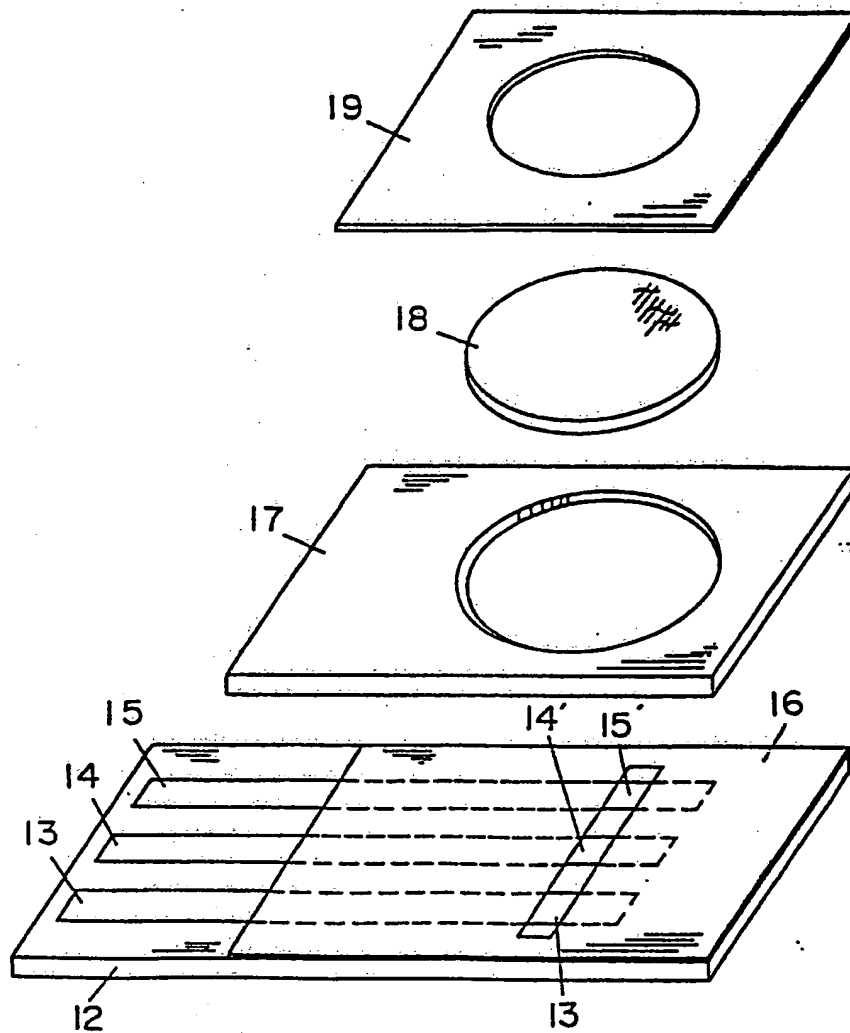


FIG. 4

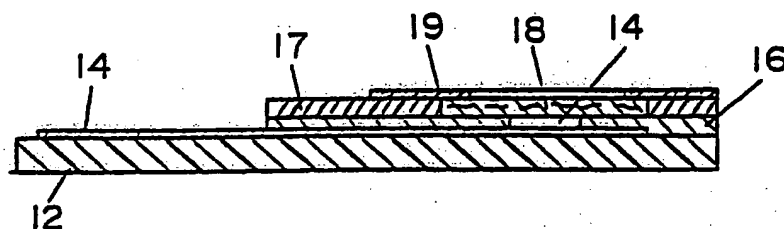
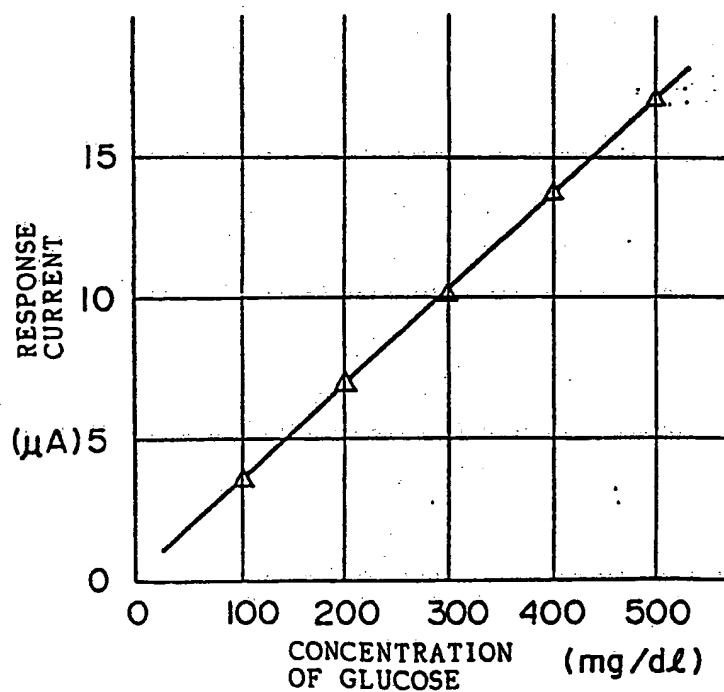


FIG. 5



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FIG. 6

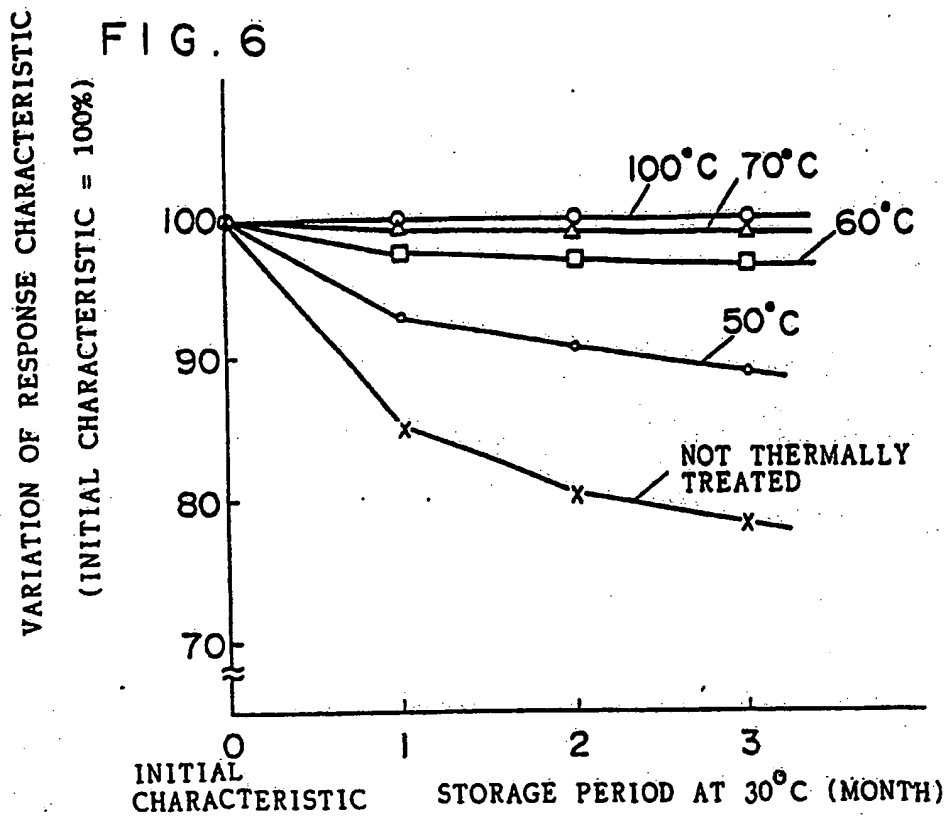


FIG. 7

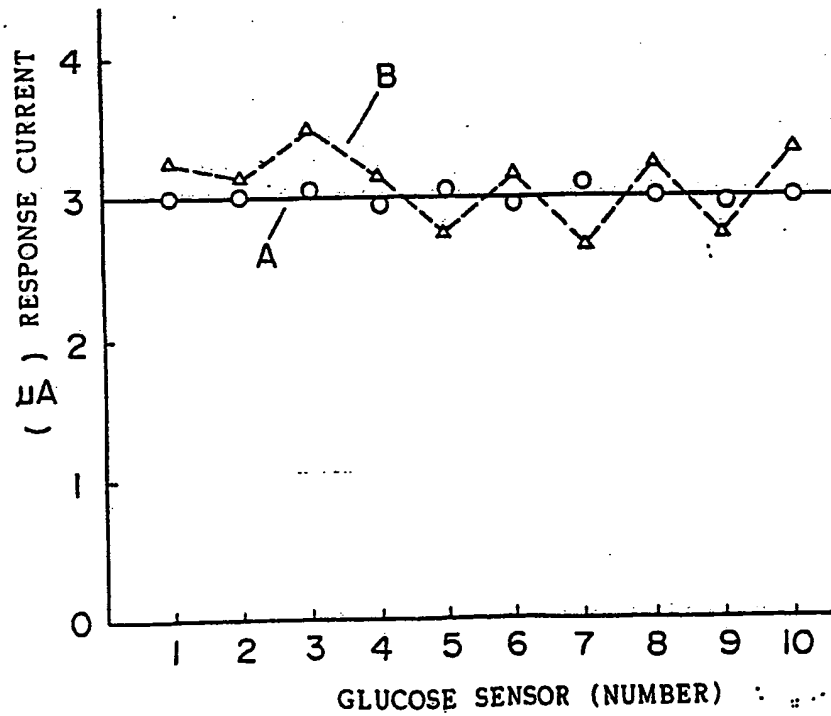


FIG. 8

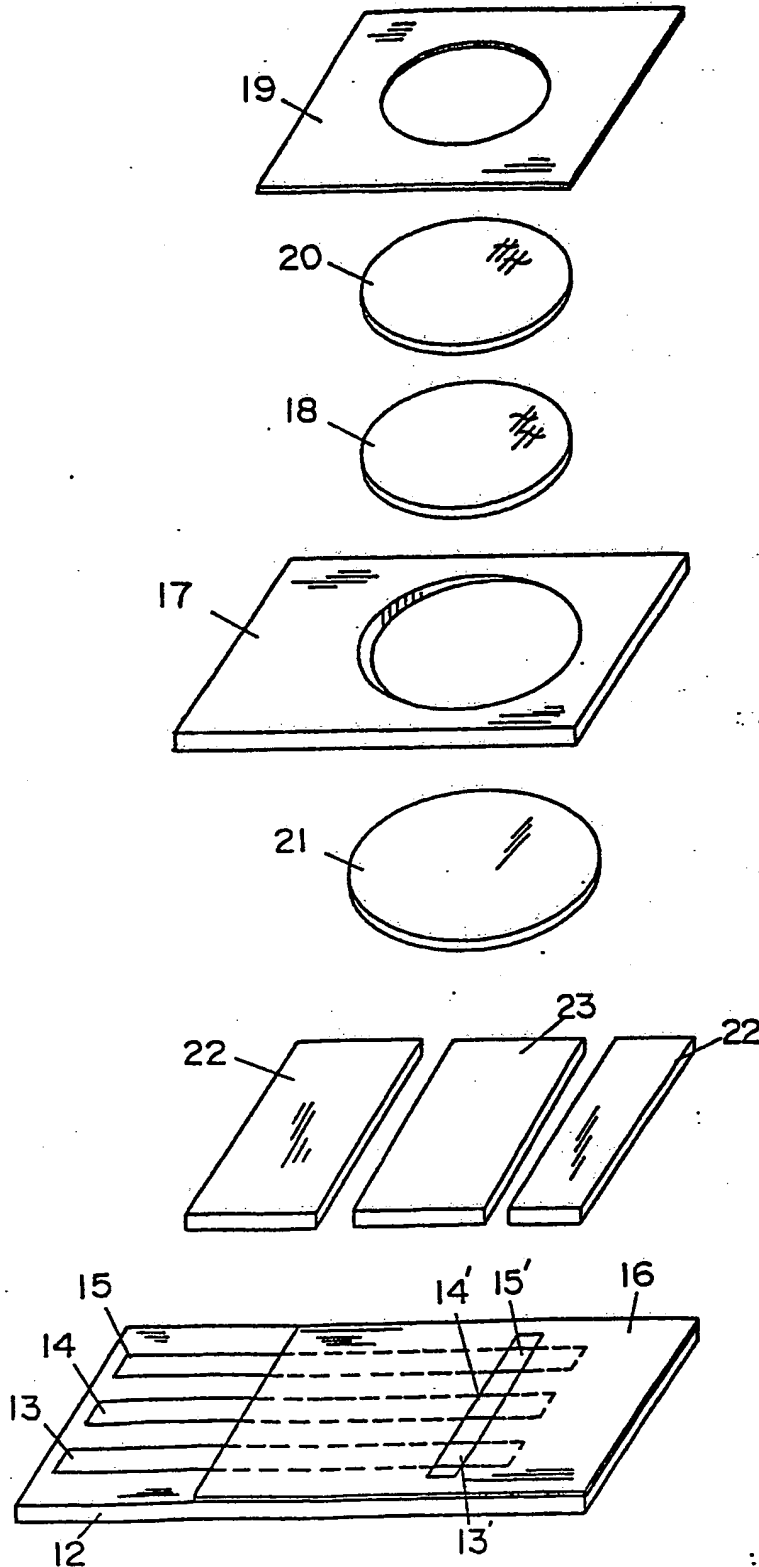
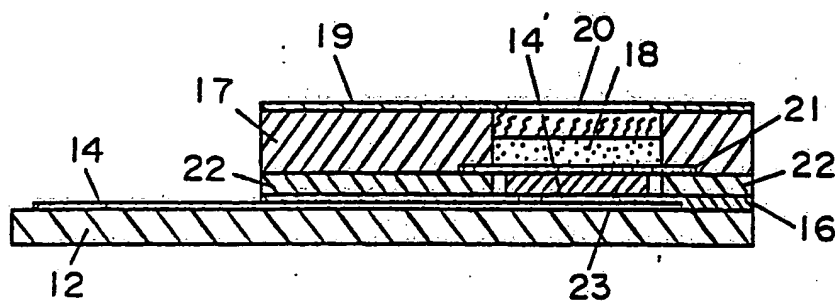


FIG. 9



LIST OF REFERENCE NUMERALS IN THE DRAWINGS:

- 1..... support
- 2..... reagent layer
- 3..... developing layer
- 4..... waterproof layer
- 5, 21..... filtration layers
- 6..... small hole
- 7..... insulative substrate
- 8, 14, 14'..... measuring electrodes
- 9, 13, 13'..... counter electrodes
- 10, 11..... leads
- 15, 15'.... reference electrodes
- 16..... insulative layer
- 17..... holding frame
- 18..... perforated body
- 19..... resin cover
- 20..... sample-accepting layer
- 22..... resin plate
- 23..... liquid-retaining layer

0230472

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP86/00311

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl ⁴ G01N27/30, G01N27/46		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
IPC	G01N27/30, 27/46	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
Jitsuyo Shinan Koho		1926 - 1986
Kokai Jitsuyo Shinan Koho		1971 - 1986
III. DOCUMENTS CONSIDERED TO BE RELEVANT **		
Category *	Citation of Document, "with indication, where appropriate, of the relevant passages" *	Relevant to Claim No. **
A	JP, A, 59-166852 (Matsushita Electric Industrial Co., Ltd.) 20 September 1984 (20. 09. 84) & WO, A, 84/03562 & EP, A, 136362	1 - 10
A	JP, A, 60-24444 (Matsushita Electric Industrial Co., Ltd.) 7 February 1985 (07. 02. 85) (Family: none)	1 - 10
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IV. CERTIFICATION		
Date of the Actual Completion of the International Search *		Date of Mailing of this International Search Report *
September 4, 1986 (04. 09. 86)		September 16, 1986 (16. 09. 86)
International Searching Authority *		Signature of Authorized Officer **
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